REMARKS

Restriction under 35 U.S.C. 121

I. Restriction and Election with Traverse

Claims 4-41, 44-114, 116-123, and 126-149 have been withdrawn without prejudice.

Claims 1, 115, 124, and 125 have been amended.

Original Claims 2, 3, 42, 43, stand ready for examination.

The Office makes a restriction of the present application and states the following:

> Applicants are required to select a single enhanced combination of one cyclooxygenase-2 inhibitor, one matrix Metalloproteinase inhibitor and antineoplastic agent for examination on the merits.

In response to the restriction, Applicants elect one inhibitor from the list of cyclooxygenase-2 inhibitors (with traverse), one inhibitor from the list of matrix metalloproteinases (with traverse), and one antineoplastic agent (without traverse).

With traverse, Applicants elect celecoxib as the single cyclooxygenase-2 inhibitor.

With traverse, Applicants elect N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl] sulfonyl]-3-thiomorpholinecarboxamide as the single matrix metalloproteinase

Without traverse, Applicants elect paclitaxel as the single antineoplastic agent for the present invention. The combination of celecoxib, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl] sulfonyl]-3-thiomorpholinecarboxamide, and paclitaxel stand ready for examination on the merits.

Support for the election of the matrix metalloproteinase inhibitor, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl] sulfonyl]-3-thiomorpholinecarboxamide, and the cyclooxygenase-2 inhibitor, celecoxib, with the antineoplastic agent, paclitaxel, is found on numerous pages throughout the application.

Support for the use of celecoxib in the present invention is found on pages 101 and 103 (Table 4), and on page 202, line 12; and page 203, line 4. Support for the use of paclitaxel in the present invention is found on page 159, line 24; page 164, line 25; page 166, line 31; page 168, lines 1 and 9; page 169, lines 11, 15, 17, and 28; page 172, line 2; and page 173, line 4. Support for the use of N-hydroxy-2,2 dimethyl-4-[[4-(4-pyridinyl-oxy)-phenyl]-sulfonyl]-3-thiomorpholinecarboxamide in the present invention is found on page 340, line 9; page 349, line 13; and page 375, line 9.

Support for the present elections can also be found in the original Claim set. Specifically, Claims 1, 21, 34(4), 37, 44(11), 55, 58, 78, 91(4), 94, 101(11), 112, 115, 116(4), 119, 123, 126(11), and 137 most clearly point out the use of the three elected species (celecoxib, N-hydroxy-2,2 dimethyl- 4-[[4-(4-pyridinyloxy)phenyl]-sulfonyl]- 3-thiomorpholinecarboxamide, and paclitaxel) for the present invention.

Support for amending Claims 115, 124, and 125 by inserting the term "therapeutic" immediately before the word "combination", can be found on page 103, lines 2, 5, 8, 11, and 14-15.

II. Reasons for traverse

Applicants respectfully traverse the restriction for the following reasons:

A. Applicants submit the elected compound, celecoxib, and the non-elected compounds of the claims comprise a single family of compounds having activity as cyclooxygenase-2 inhibitors. The unifying feature of this class of compounds is the cyclooxygenase-2 inhibitory activity, which is common to all cyclooxygenase-2 inhibitors of the present

invention. Representative compounds of the defined family possess cyclooxygenase-2 activity, as described in the present application on page 95, line 22 through page 96, line 9. The phrase reads as follows:

> "COX-2 inhibitor" or "cyclooxygenase-II inhibitor" includes agents that specifically inhibit a class of enzymes, cyclooxygenase-2, with less significant inhibition of cyclooxygenase-1. Preferably, it includes compounds which have a cyclooxygenase-2 IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM.

Therefore, the cyclooxygenase-2 compounds are not independent and distinct, each from the other. Accordingly, the Applicants assert that no restriction is appropriate among the compounds recited, and respectfully request that the Restriction Requirement for the cyclooxygenase-2 inhibitors be withdrawn.

Similarly, the Applicants submit that the matrix metalloproteinase inhibitors are not independent and distinct, each from the other. Applicants submit the elected compound, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]- 3-thiomorpholine carboxamide and the non-elected compounds of the claims comprise a single family of compounds having activity as matrix metalloproteinase inhibitors.

The unifying feature of this class of compounds is their matrix metalloproteinase enzyme inhibitory activity, which is common to all matrix metalloproteinase inhibitors of the present invention. Representative compounds of the defined family possess matrix Metalloproteinase enzyme inhibitory activity, as described in the present application on page 33, lines 17-22, which reads as follows:

> The phrase "matrix metalloproteinase inhibitor" or "MMP inhibitor" includes agents that specifically inhibit a class of enzymes, the zinc metalloproteinases (metalloproteases). The zinc metalloproteinases are involved in the degradation of connective tissue or connective tissue components.

Therefore, the matrix metalloproteinase inhibitors are not independent and distinct, each from the other. Accordingly, the Applicants assert that no restriction is appropriate among the compounds recited (for the cyclooxygenase-2 inhibitors and for the matrix metalloproteinase inhibitors, and respectfully request that the Restriction Requirement for these to be withdrawn.

III. Election is without prejudice

Applicants submit that the provisional election of paclitaxel from the list of antineoplastic agents, and celecoxib from the list of cyclooxygenase-2 inhibitors, and N-hydroxy-2,2 dimethyl-4-[[4-(4-pyridinyl-oxy)-phenyl]-sulfonyl]-3-thiomorpholine-carboxamide, from the list of matrix Metalloproteinase inhibitors, is without prejudice to Applicants' right to file divisional applications directed to the subject matter not contained therein.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, he is cordially invited to contact Applicant's representative at the below listed number.

Respectfully submitted,

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